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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/743,740	12/24/2003	Eiichi Iishi	1422-0619P	9686

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EXAMINER	
HABTE, KAHSAY	

ART UNIT	PAPER NUMBER
1624	

DATE MAILED: 11/25/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Advisory Action Before the Filing of an Appeal Brief	**Application No.** 10/743,740	**Applicant(s)** IISHI ET AL.	
	Examiner Kahsay Habte, Ph. D.	**Art Unit** 1624	

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 03 November 2005 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE.

1. ☒ The reply was filed after a final rejection, but prior to or on the same day as filing a Notice of Appeal. To avoid abandonment of this application, applicant must timely file one of the following replies: (1) an amendment, affidavit, or other evidence, which places the application in condition for allowance; (2) a Notice of Appeal (with appeal fee) in compliance with 37 CFR 41.31; or (3) a Request for Continued Examination (RCE) in compliance with 37 CFR 1.114. The reply must be filed within one of the following time periods:
   a) ☐ The period for reply expires _____months from the mailing date of the final rejection.
   b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.

   Examiner Note: If box 1 is checked, check either box (a) or (b). ONLY CHECK BOX (b) WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

NOTICE OF APPEAL

2. ☒ The Notice of Appeal was filed on *03 November 2005*. A brief in compliance with 37 CFR 41.37 must be filed within two months of the date of filing the Notice of Appeal (37 CFR 41.37(a)), or any extension thereof (37 CFR 41.37(e)), to avoid dismissal of the appeal. Since a Notice of Appeal has been filed, any reply must be filed within the time period set forth in 37 CFR 41.37(a).

AMENDMENTS

3. ☐ The proposed amendment(s) filed after a final rejection, but prior to the date of filing a brief, will not be entered because
   (a) ☐ They raise new issues that would require further consideration and/or search (see NOTE below);
   (b) ☐ They raise the issue of new matter (see NOTE below);
   (c) ☐ They are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or
   (d) ☐ They present additional claims without canceling a corresponding number of finally rejected claims.

   NOTE: _____. (See 37 CFR 1.116 and 41.33(a)).
4. ☐ The amendments are not in compliance with 37 CFR 1.121. See attached Notice of Non-Compliant Amendment (PTOL-324).
5. ☐ Applicant's reply has overcome the following rejection(s): _____.
6. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).
7. ☒ For purposes of appeal, the proposed amendment(s): a) ☐ will not be entered, or b) ☐ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.

   The status of the claim(s) is (or will be) as follows:
   Claim(s) allowed: _____.
   Claim(s) objected to: _____.
   Claim(s) rejected: *1-3*.
   Claim(s) withdrawn from consideration: _____.

AFFIDAVIT OR OTHER EVIDENCE

8. ☐ The affidavit or other evidence filed after a final action, but before or on the date of filing a Notice of Appeal will not be entered because applicant failed to provide a showing of good and sufficient reasons why the affidavit or other evidence is necessary and was not earlier presented. See 37 CFR 1.116(e).
9. ☐ The affidavit or other evidence filed after the date of filing a Notice of Appeal, but prior to the date of filing a brief, will not be entered because the affidavit or other evidence failed to overcome all rejections under appeal and/or appellant fails to provide a showing a good and sufficient reasons why it is necessary and was not earlier presented. See 37 CFR 41.33(d)(1).
10. ☐ The affidavit or other evidence is entered. An explanation of the status of the claims after entry is below or attached.

REQUEST FOR RECONSIDERATION/OTHER

11. ☒ The request for reconsideration has been considered but does NOT place the application in condition for allowance because: See memo.
12. ☐ Note the attached Information Disclosure Statement(s). (PTO/SB/08 or PTO-1449) Paper No(s). _____
13. ☐ Other: _____.

ADVISORY ACTION

1. Claims 1-3 are pending in this application.

2. The amendment filed 11/3/2005 under 37 CFR 1.116 in reply to the final rejection (5/9/2005) will be entered, but is not deemed to place the application in condition for allowance. Applicants have not amended the claims or presented an argument that is persuasive to overcome the 102(b) rejection raised in previous Office Action (see item 3).

Applicants argue, "[t]he crystals disclosed by Kaspersen et al. are those of '^{13}C-compound'. Therefore, crystals of unlabeled mirtazapine of the present invention are quite different from those disclosed by Kaspersen et al. ". Applicants also argue that the whole disclosure of the present specification, the compound of the present invention is unlabeled compound, which is useful as an antidepressant for therapeutic applications to human bodies.....To the contrary, Kaspersen et al. disclose a ^{13}C-labeled compound for metabolic studies." The examiner disagrees with applicants. The labeled and unlabeled mirtazapine crystals are not significantly different one from the other. Carbon 13 has the natural abundance of 1%; that is, approximately 1% of all the carbon atoms in any sample of an organic compound are carbon-13 atoms. Note that Kaspersen's labeled compound was prepared in order to study what the known unlabeled compound does in the body. The use of labeled compound in research is in fact based on the assumption that they act the same as non-labeled. As far as we know, the labeled and

unlabeled crystal mirtazapine compounds can be administered to the body for treatment purposes.

Applicants also argue that Kaspersen's unlabeled compound is clearly distinguished from the unlabeled compound because it is denoted as "Org 3770" and a "^{13}C-labeled compound".....and also the melting point of Kaspersen's compound 1c has a melting point of 123.8-125.8 °C that is different from their compounds that has a melting point of 114-116 °C. The examiner disagrees with applicant's arguments. First of all, naming a labeled compound as "Org-3770" or something else does not make it different from the unlabeled compound. Note that a same compound can have 10 names. In regard to the melting point, applicants have to replicate Kaspersen and show that their compounds are different from Kaspersen's. Melting point difference by itself cannot be used to prove that applicant's mirtazapine crystals are different from that of Kaspersen's, unless it is coupled with other evidences. Applicants have to prove that the drying conditions of Kaspersen et al. would not necessarily provide mirtazapine crystals having (i) a water content of not more than 0.5% by weight and (ii) a hygroscopic degree of not more than 0.6% by weight when the crystals are stored in the air having a relative humidity of 75% at 25°C under atmospheric pressure for 500 hours. Applicants failed to address this issue (replicating) that is raised in previous Office Action. Applicants simply state, "the disclosure of Kaspersen et al. is not sufficiently close to the presently claimed invention". Applicants further argue, "[i]t makes no sense to follow the Examiner's suggestion and repeat the drying process of Kaspersen's since the drying process of Kaspersen et al. would provide a dried labeled composition. Such

a dried labeled composition is irrelevant to the claimed invention having an isotope in a naturally occurring ratio". The examiner disagrees with this argument. As shown above labeled and unlabeled mirtazapine are not significantly different one from the other, thus, the drying process of labeled or unlabeled composition would be presumed to be the same. Applicants can overcome the rejection over the prior art by showing that their product (unlabeled) is different from Kaspersen's.

Applicants also argue: "Kaspersen et al. do not disclose or suggest hemihydrate mirtazapine heated to dry at a temperature higher than ordinary heating temperatures. Therefore, the low-hygroscopic anhydrous mirtazapine crystals of the present invention cannot be expected from Kaspersen et al.". The examiner disagrees with this argument. Applicants are not claiming hemihydrate mirtazapine, but a low-hygroscopic anhydrous mirtazapine crystals having (i) water content of not more than 0.5% by weight and (ii) a hygroscopic degree of not more than 0.6% by weight when crystals are stored in the air having a relative humidity of 75% at 25% under atmospheric pressure for 500 hours. Thus, the argument that has to do with "hemihydrate" is irrelevant. In regard to the conclusion by applicants "[t]hat the low-hygroscopic anhydrous mirtazapine crystals of the present invention cannot be expected from Kaspersen et al.", the examiner disagrees with this conclusion. Applicants are simply speculating the outcome of a reaction.

Applicants further point out to a document "Extract from Hunnius Pharmazeutisches Worterbuch, 8th Edition, de Gruyter 1998, page 682, that discloses "Water of hydration: Water as a structural element of the crystal lattice of a substance;

due to the strong fixation removal of the water of hydration is only possible by higher temperatures with destruction of crystal" and conclude that "Therefore, it cannot be expected that anhydrous crystals are obtained by heating the hydrate or hemi hydrate of crystals at high temperatures, because a person skilled in the art would usually avoid heating the crystals at high temperatures". The examiner disagrees with applicant's conclusion. Applicants have to show this by replicating Kaspersen and present the data in declaration form. Applicants seem to predict the outcome of a reaction (e.g. drying) without actually doing the reaction.

Applicants argue that "[e]ven if the compound 1c disclosed by Kaspersen et al. is low-hygroscopic anhydrous mirtazapine, the compound 1c is not unlabeled"...."[e]ven if the crystals of label compound by Kaspersen et al. are hydrate, the crystals of the mirtazapine hydrate of the present invention cannot be expected from Kaspersen et al., because the mirtazapine hydrate of the present invention is not labeled compound as disclosed by Kaspersen et al. but an unlabeled compound". The examiner disagrees with applicants. As shown above, the labeled and unlabeled mirtazapine crystals are not significantly different one from the other since carbon 13 has the natural abundance of 1%; that is, approximately 1% of all the carbon atoms in any sample of an organic compound are carbon-13 atoms. Thus, it is presumed that Kaspersen's labeled or Kaspersen's hydrated mirtazapine to be the same as applicant's low-hygroscopic unlabeled mirtazapine or hydrated labeled mirtazapine. Note that both applicants and Kaspersen use an extremely similar method, thus, it is presumed that the same hydrate product is formed from virtually the same crystallization method. Kaspersen *et al.* on

page 1066 teaches the synthesis of mirtazapine and the crystallization of the mirtazapine (compound **1c**) from the crude product using charcoal, methanol/water solvent mixture to achieve colorless crystals. Applicants on page 6 (lines 5-6) also discloses mixed solvents such as methanol/water, plus charcoal to make crystals of a mirtazapine hydrates. The only difference between applicant's mirtazapine and Kaspersen's Org-3770 is that Kaspersen's compound **1c** is ^{13}carbon labeled, but the instantly claimed product requires that the mirtazapine be unlabeled. One skilled in the art would presume that labeled and unlabelled would crystallize in the same way. The compound is asserted to be inherently a hydrate because it is made via a method which applicants use to prepare hydrate.

According to MPEP 2112.01:

> *Where the claimed and prior art products are identical or substantially identical in* structure or composition, or are produced by identical or substantially identical processes, a prima facie case of either anticipation or obviousness has been established. In re Best, 562 F.2d 1252, 1255, 195 USPQ 430, 433 (CCPA 1977). "When the PTO shows a sound basis for believing that the products of the applicant and the prior art are the same, the applicant has the burden of showing that they are not." In re Spada, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). *[underscoring added]*

Therefore, the prima facie case can be rebutted by evidence showing that the prior art products do not necessarily possess the characteristics of the claimed product. In re Best, 562 F.2d at 1255, 195 USPQ at 433.

Since the hydrate of the labeled compounds could just as well be important intermediates for preparing anhydrous labeled mirtazapine crystals and the fact that the hydrates are the conventional way of making pharmaceutical formulation as shown above, the rejection is proper.

The period for reply continues to run 3 MONTHS from the date of the final rejection. Any extension of time must be obtained by filing a petition under 37 CFR 1.136(a) accompanied by the appropriate fee. The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. A reply within the meaning of 37 CFR 1.113 or a request for a continued examination (RCE) in compliance with 37 CFR 1.114 must be timely filed to avoid abandonment of this application.

Conclusion

3. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kahsay Habte, Ph. D. whose telephone number is (571) 272-0667. The examiner can normally be reached on M-F (9.00AM- 5:30PM).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Wilson can be reached at (571) 272-0661. The fax phone number for the organization where this application or proceeding is assigned is (571)-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Kahsay Habte
Patent Examiner
Art Unit 1624

KH
November 18, 2005